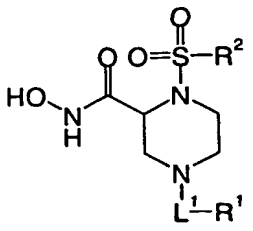
We claim:

1. A compound of structural formula **I**:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein

L^1 is $-C(O)-$, $-S(O)_2-$, or $-(CH_2)_n-$;

R^1 is $-H$, $-OR^{11}$, $-(CH_2)_nR^{11}$, $-C(O)R^{11}$, or $-NR^{12}R^{13}$;

R^{11}, R^{12}, and R^{13} independently are

g) R^{50};

h) saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R^{50} substituents;

i) C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or $-C(O)H$, each of which is optionally substituted with one, two or three substituents independently selected from R^{50} and saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R^{50} substituents;

or R^{12} and R^{13} together with the N to which they are covalently bound, a C_5-C_6 heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R^{50} substituents;

R^2 is $-R^{21}-L^2-R^{22}$;

R^{21} is saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or

fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents;

L^2 is -O-, -C(O)-, $-CH_2-$, -NH-, $-S(O_2)-$ or a direct bond;

R^{22} is saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three R^{50} substituents; and

R^{50} is R^{51}-L^3-$(CH_2)_n$-;

L^3 is -O-, -NH-, $-S(O)_{0-2}-$, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, $-C_6H_4-$, or a direct bond;

R^{51} is -H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, mono-C_1-C_6alkyl amino, di-C_1-C_6alkyl amino, -SH, $-CO_2H$, -CN, $-NO_2$, $-SO_3H$, or a saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

2. The compound according to claim 1, wherein L^1 is -C(O)- or $-S(O)_2-$.

3. The compound according to claim 2, wherein L^1 is -C(O)- and R^1 is $-OR^{11}$ or $-(CH_2)_nR^{11}$, -OC_1-C_6alkyl-mono-C_1-C_6alkyl amino, -OC_1-C_6alkyl-di-C_1-C_6alkyl amino, -OC_1-C_6alkyl-N-heterocyclyl, -C_1-C_6alkyl-mono-C_1-C_6alkyl amino, -C_1-C_6alkyl-di-C_1-C_6alkyl amino, or -C_1-C_6alkyl-N-heterocyclyl.

4. The compound according to claim 2, wherein, R^1 is C_1-C_6-alkoxy-C_1-C_6-alkoxy.

5. The compound according to claim 2, wherein R^1 is methoxyethoxy.

6. The compound according to claim 3, wherein L^1 is $-S(O)_2-$, and R^1 is $-NR^{12}R^{13}$, $-(CH_2)_nR^{11}$, $-C_1-C_6$alkyl-mono-C_1-C_6alkyl amino, $-C_1-C_6$alkyl-di-C_1-C_6alkyl amino, or $-C_1-C_6$alkyl-N-heterocyclyl.

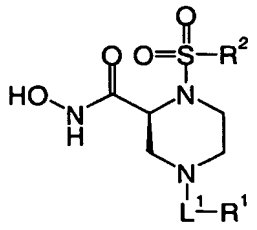
7. The compound according to claim 3, wherein L^2 is -O-.

8. The compound according to claim 7, wherein, R^2 is phenoxyphenyl wherein each phenyl is optionally substituted with one or two R^{50} substituents. In a more specific example, the R^{50} substituents are halo.

9. The compound according to claim 8, wherein the saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl containing one or two annular heteroatoms per ring is selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, furyl, thienyl, pyranyl, isobenzofuranyl, chromenyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

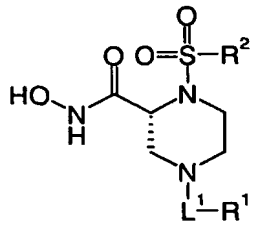
10. The compound according to claim 8, wherein R^{12} and R^{13}, together with the N to which they are covalently bound, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, pyrrolyl, imidazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, oxadiazolyl, indolyl, quinolinyl, carbazolyl, acrydinyl, and furazanyl, optionally substituted with one or two R^{50} substituents.

11. The compound according to claim 1, comprising the absolute stereochemistry of structural formula **II**:



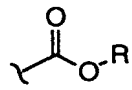
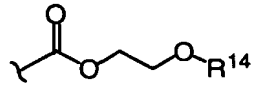
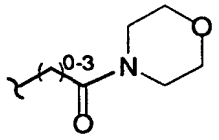
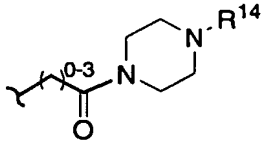
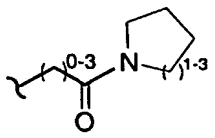
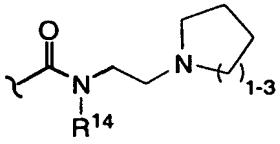
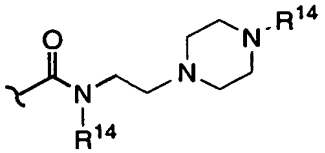
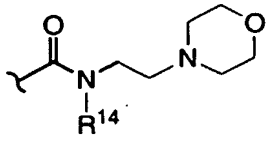
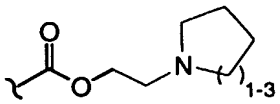
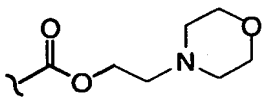
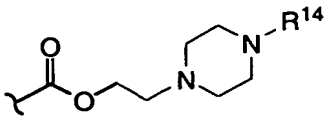
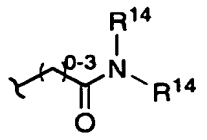
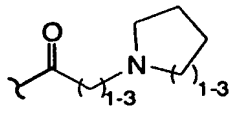
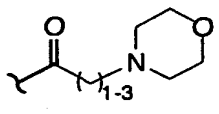
II

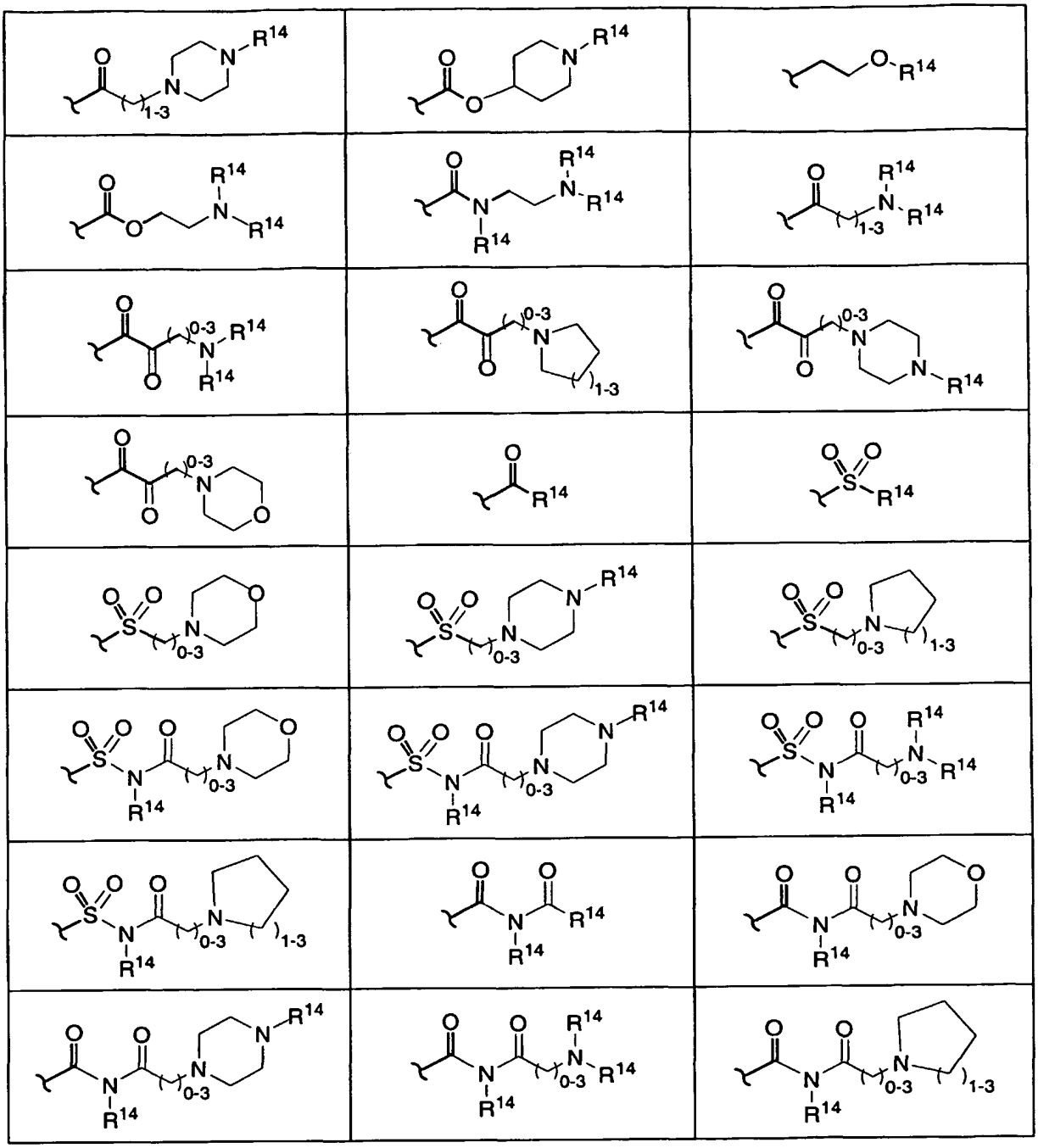
12. The compound according to claim 1, comprising the absolute stereochemistry of structural formula **III**:



III

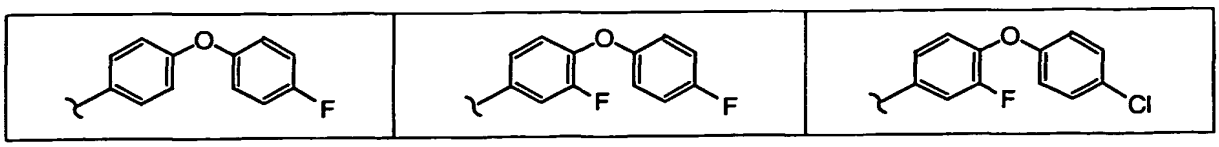
13. The compound according to claim 1, wherein $-L^1-R^1$ is selected from:

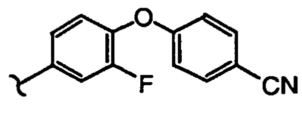
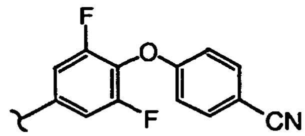
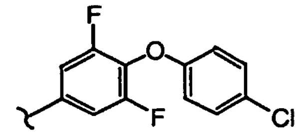
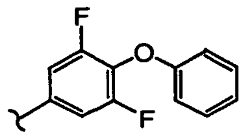
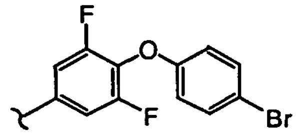
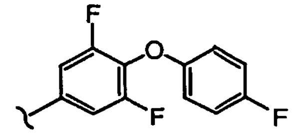
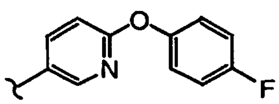
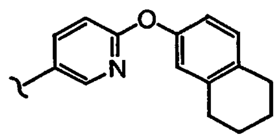
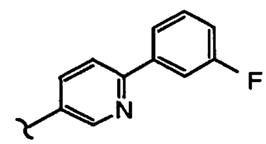
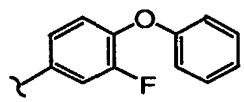
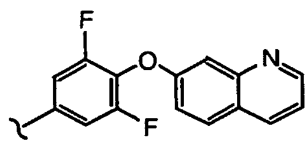
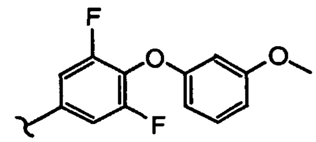
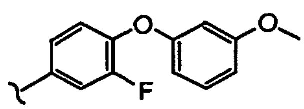
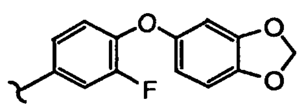
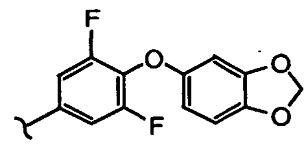
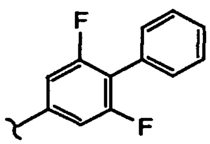
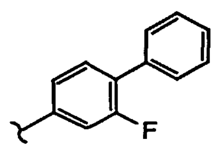
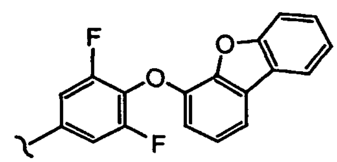
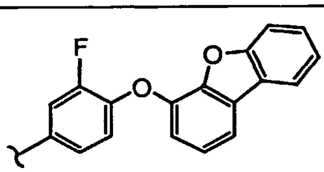
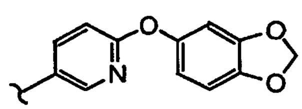
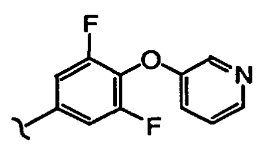
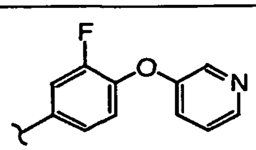
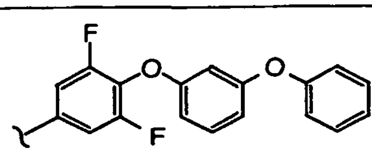
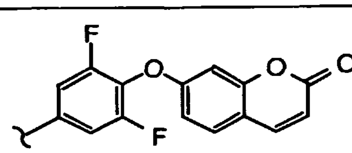
$-R^{14}$		
		
		
		
		



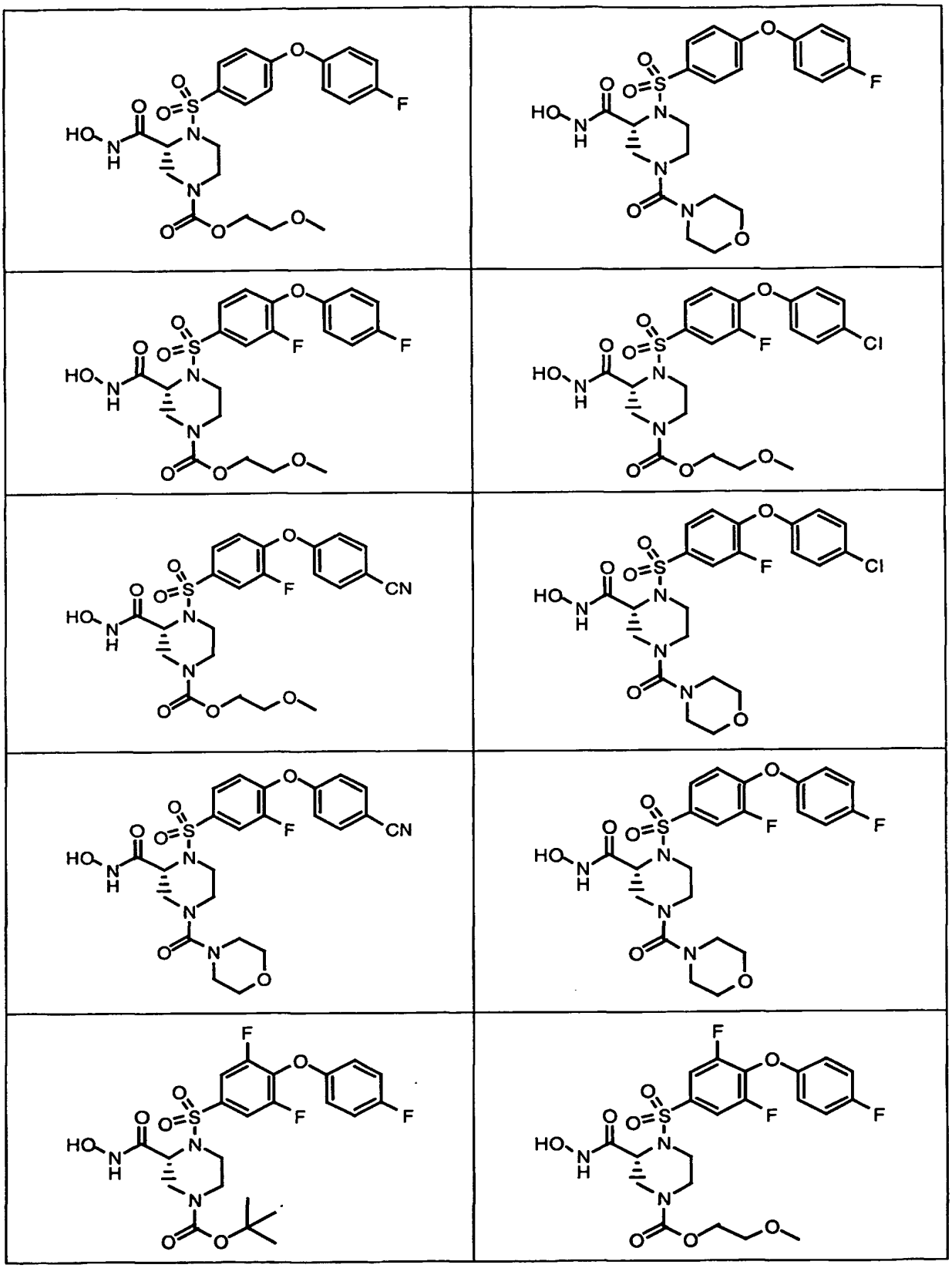
wherein each R^{14} is independently selected from -H, $-(CH_2)_{1-3}CO_2H$, alkyl, alkoxy, alkenyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; and

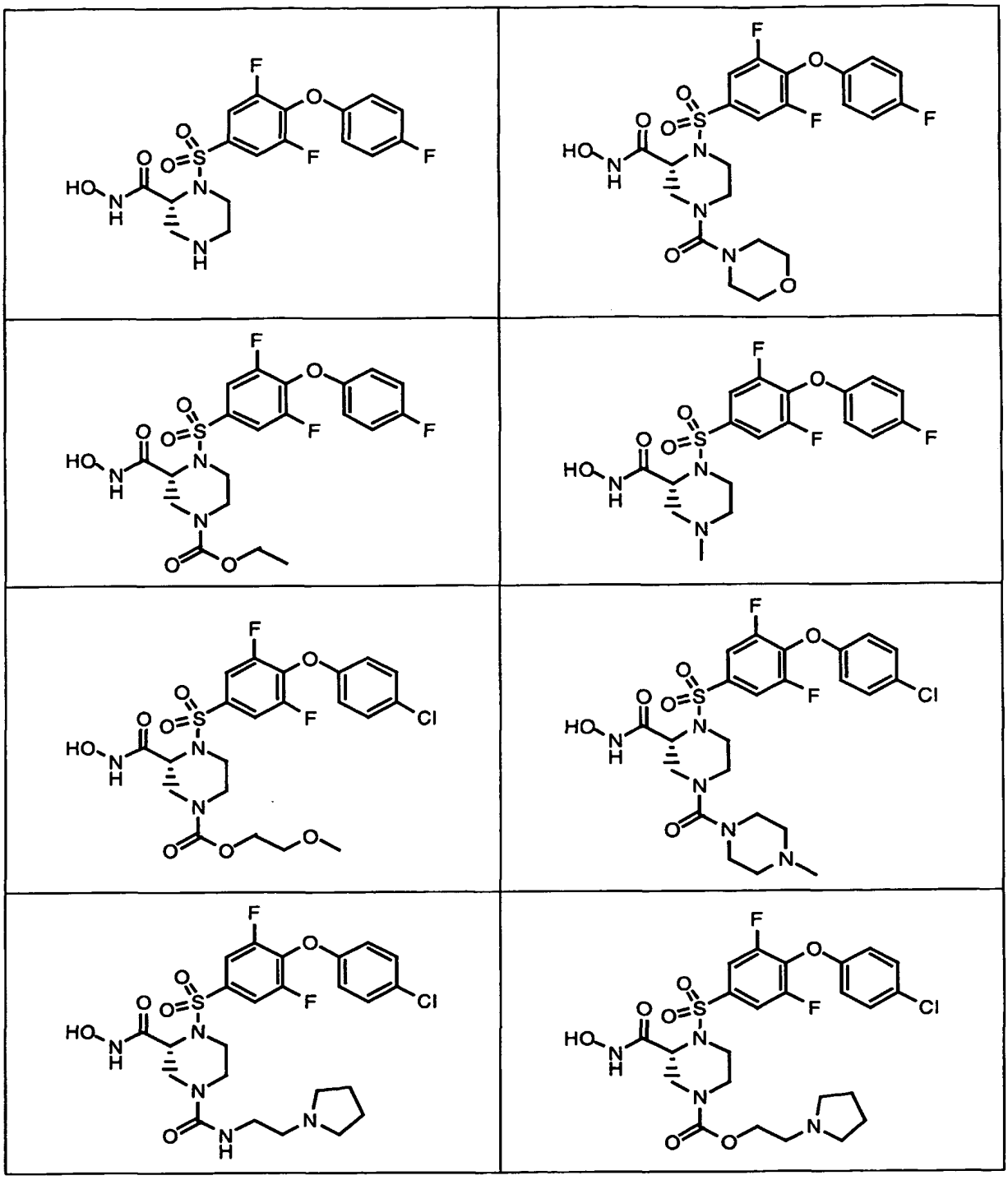
R^2 is selected from:

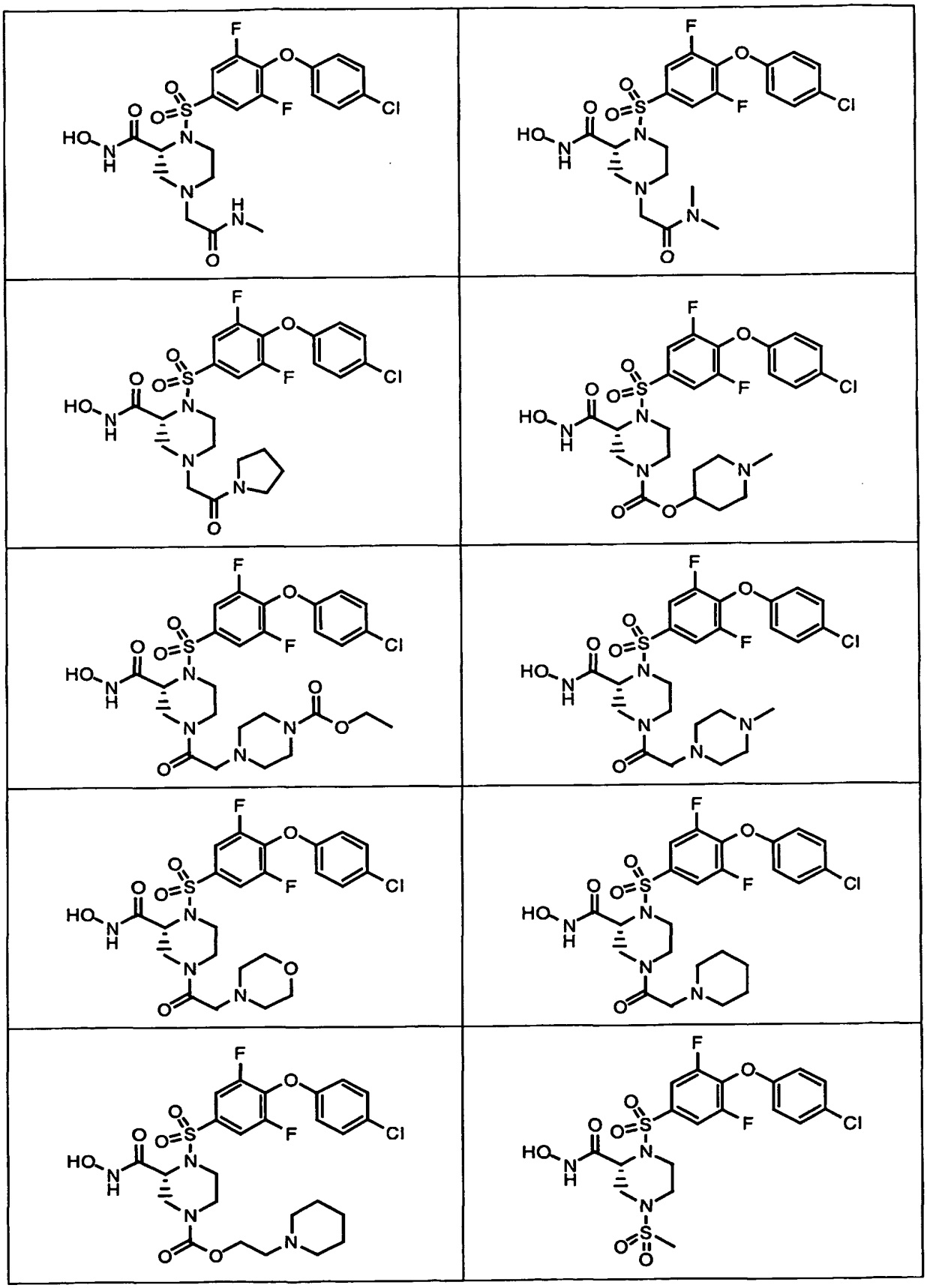


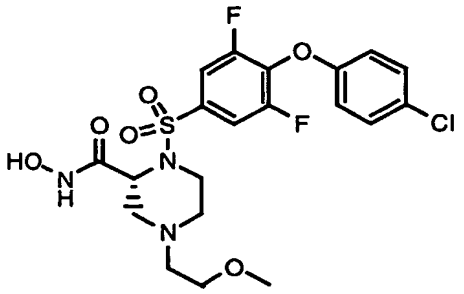
		
		
		
		
		
		
		
		

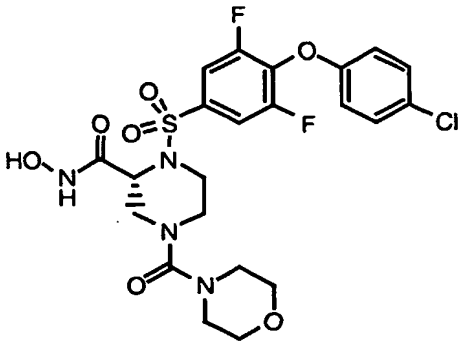
14. The compound according to claim 1, selected from:

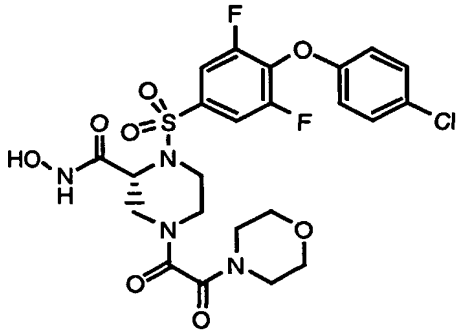


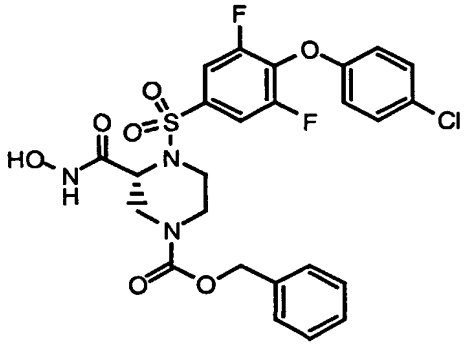


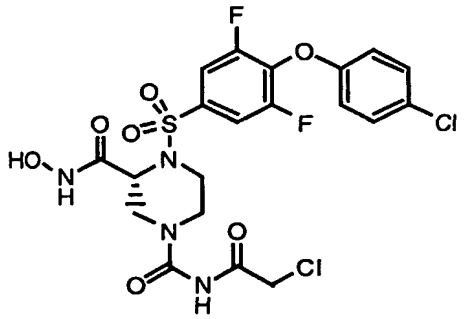


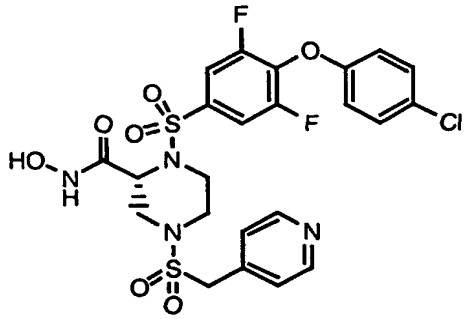


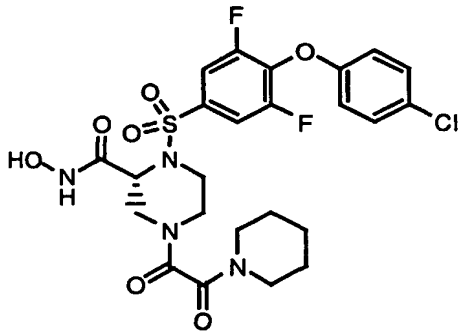


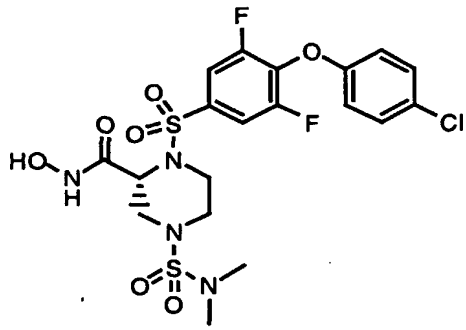


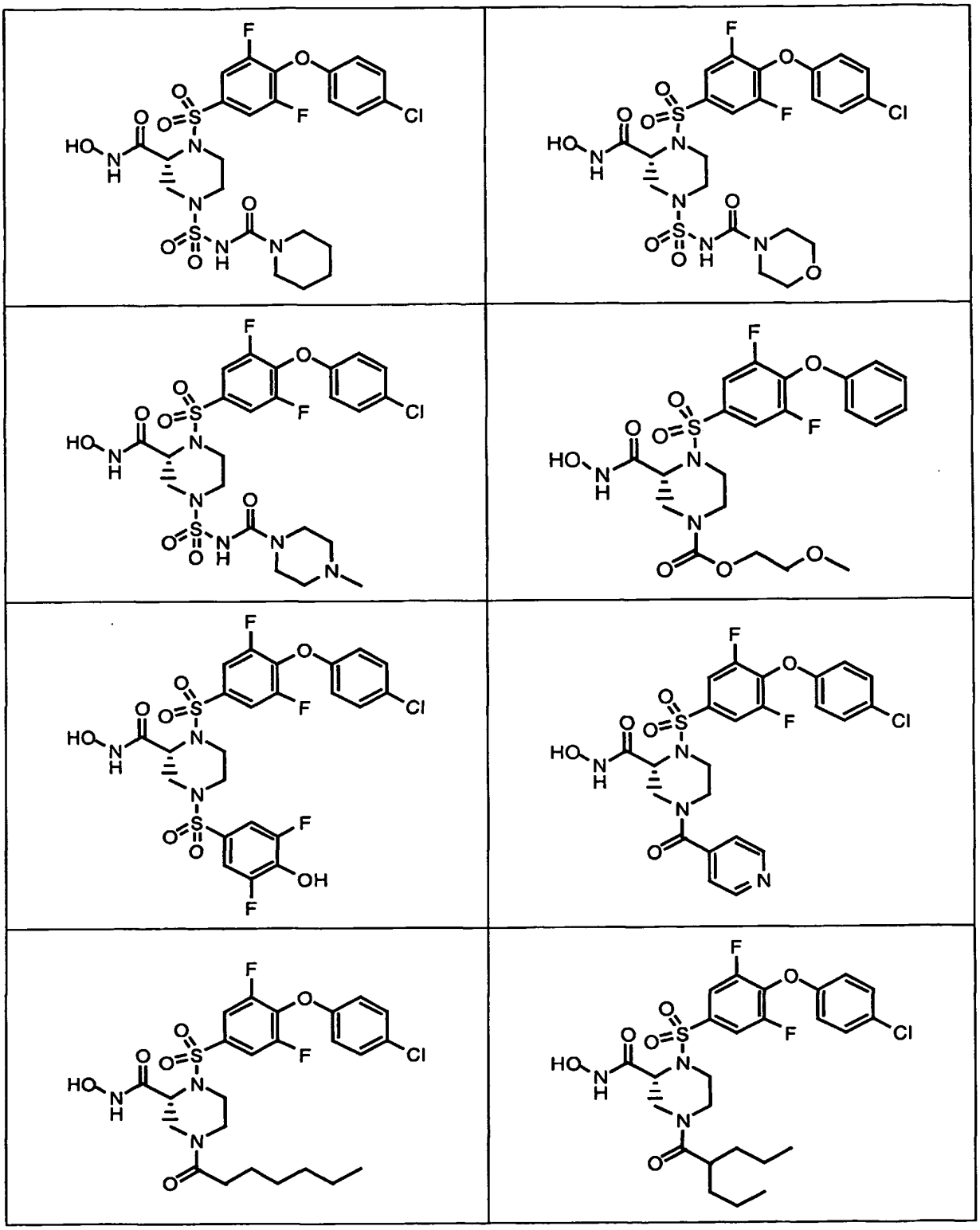


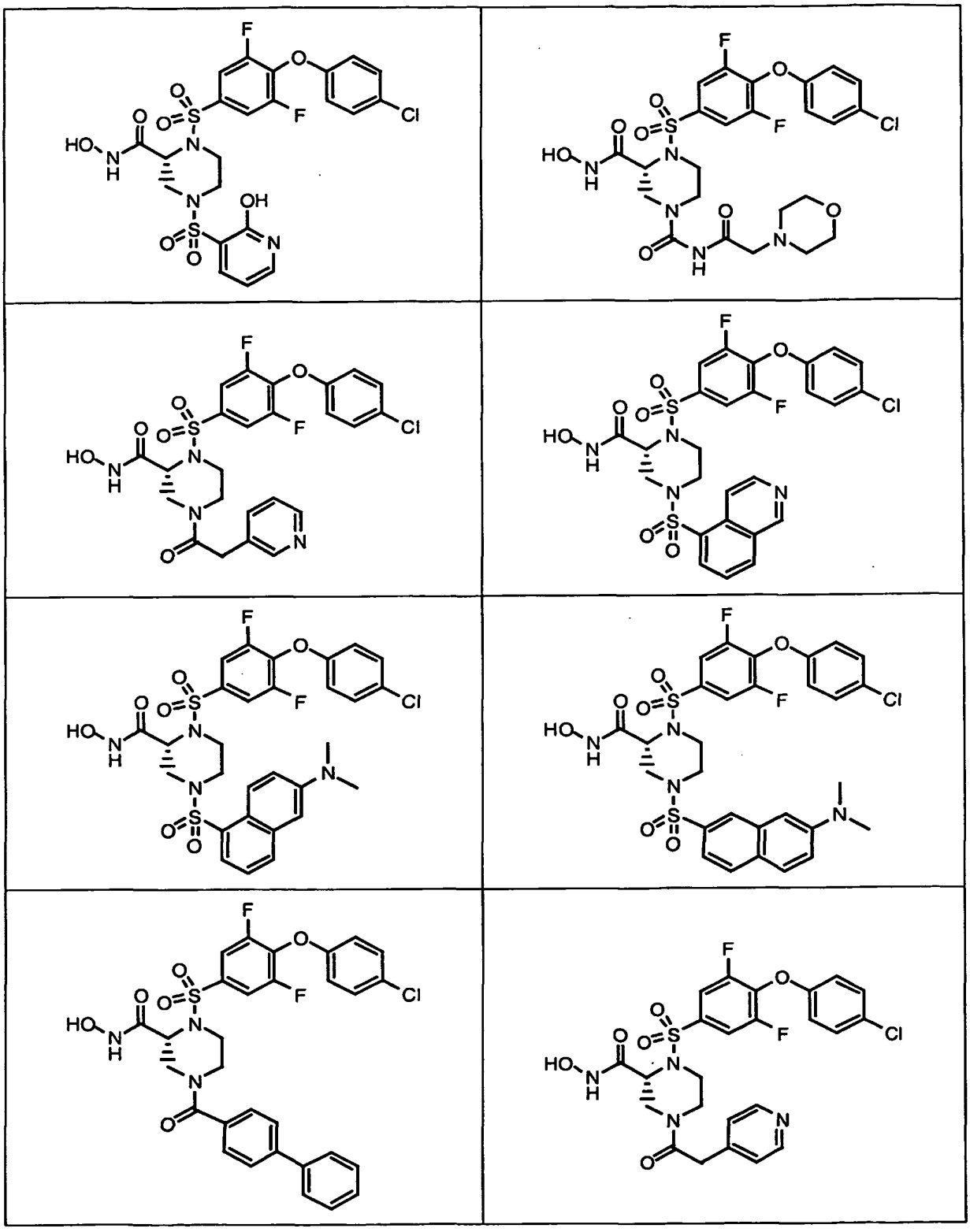


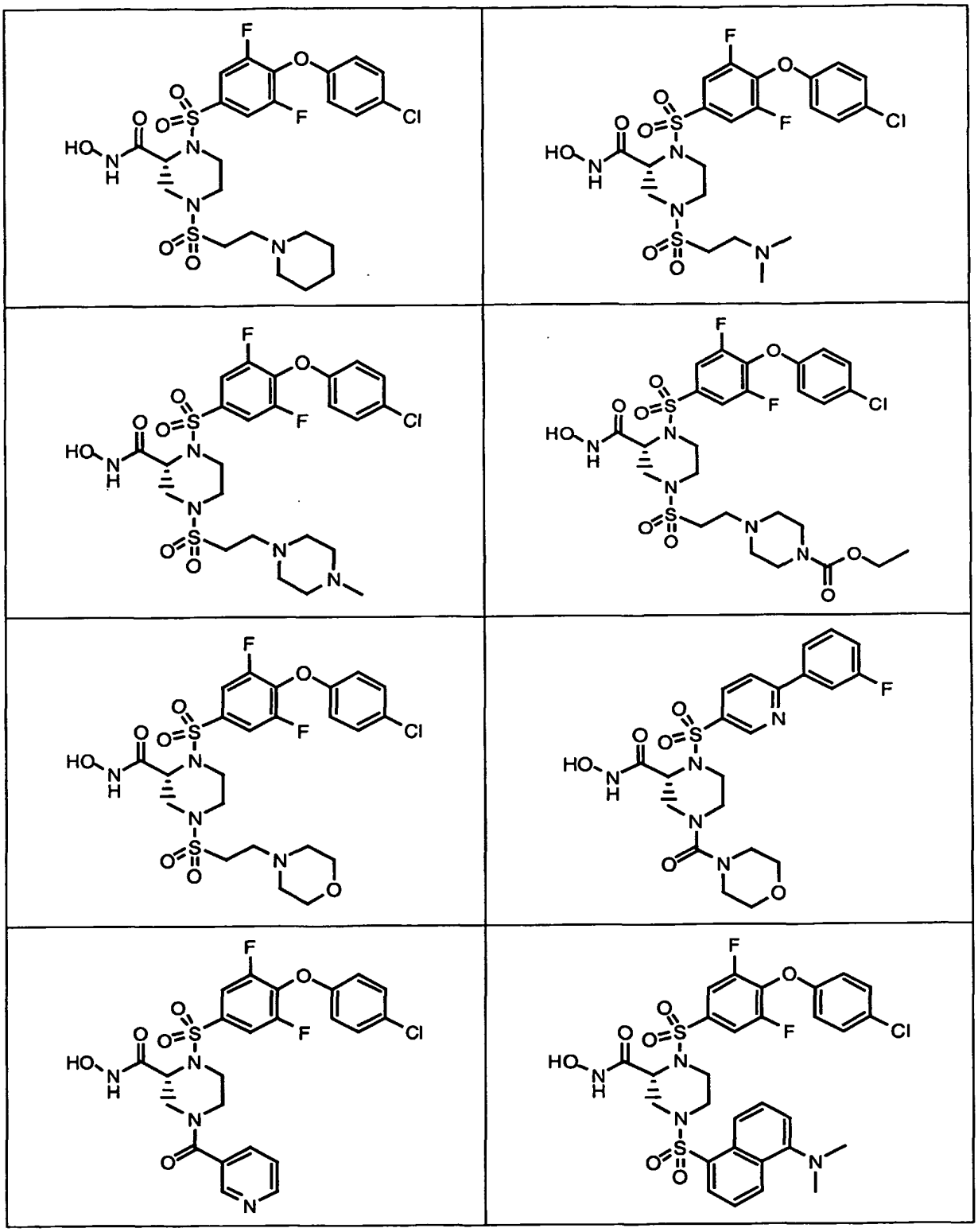


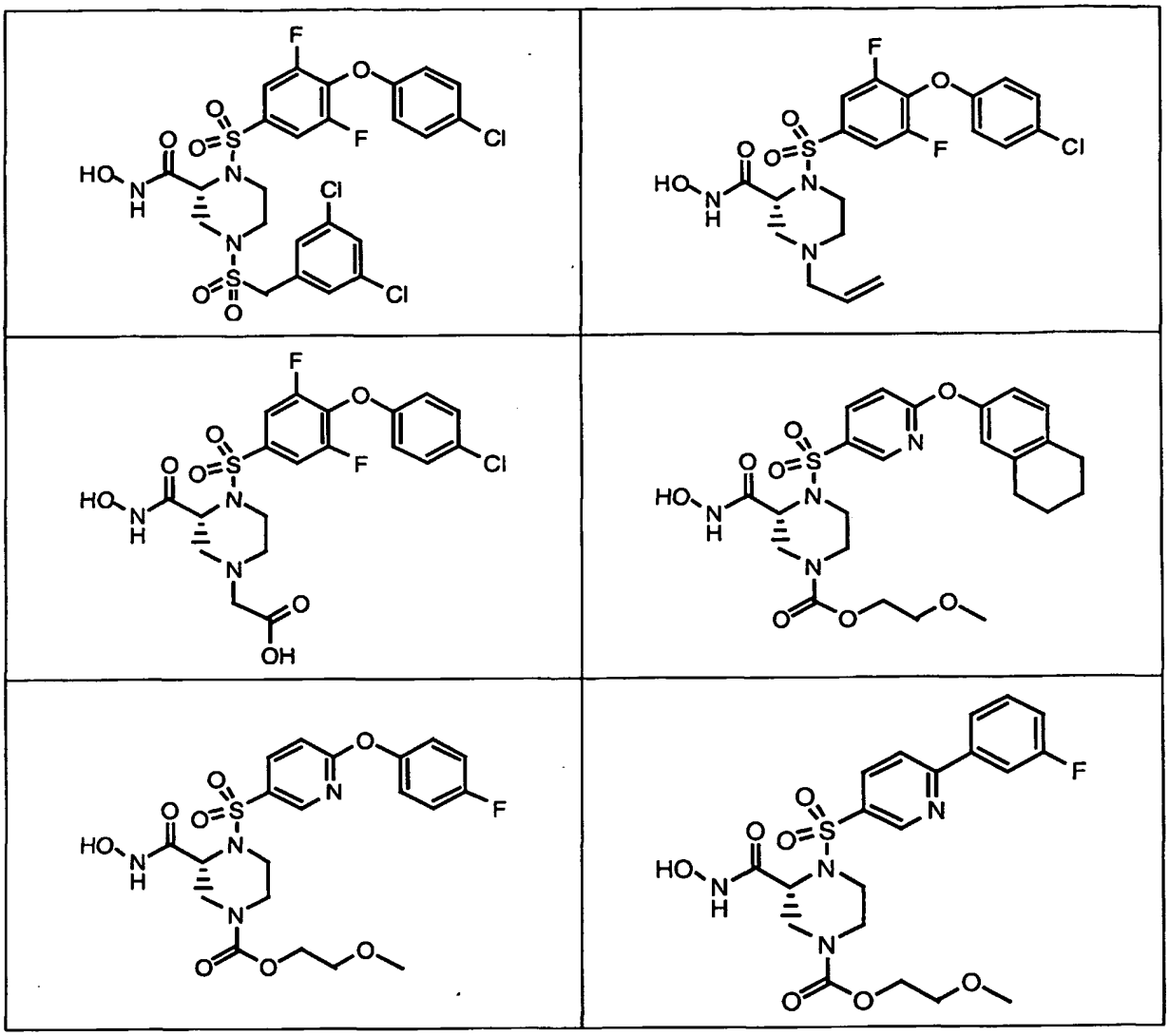




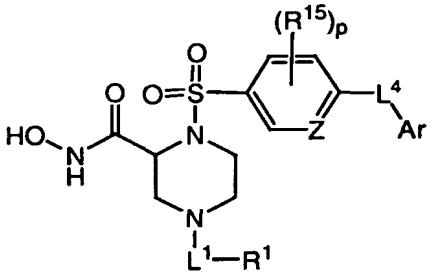








15. A compound according to formula **IV**,



IV

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof wherein,

Z is $-C(R^{15})=$, $-C(H)=$, or $-N=$;

Ar is aryl or heteroaryl, each optionally substituted;

R^{15} is fluoro;

p is 0, 1, 2, or 3;

L^1 is $-C(O)-$, $-S(O)_2-$, or $-(CH_2)_n-$;

L^4 is nothing or $-O-$;

R^1 is $-H$, $-OR^{11}$, $-(CH_2)_nR^{11}$, $-C(O)R^{11}$, or $-NR^{12}R^{13}$;

R^{11}, R^{12}, and R^{13} independently are

j) R^{50};

k) saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one or two R^{50} substituents;

l) C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or $-C(O)H$, each of which is optionally substituted with one, two or three substituents independently selected from R^{50} and saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two or three R^{50} substituents;

or R^{12} and R^{13} together with the N to which they are covalently bound, a C_5-C_6 heterocycle optionally containing a second annular heteroatom and optionally substituted with one or two R^{50} substituents; and

R^{50} is R^{51}-L^3-$(CH_2)_n-$;

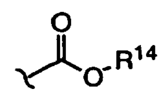
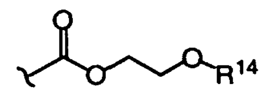
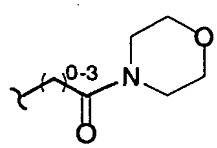
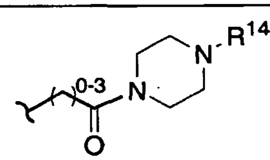
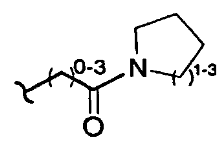
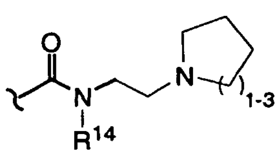
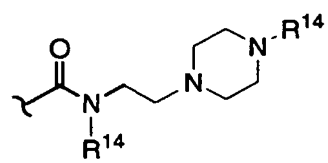
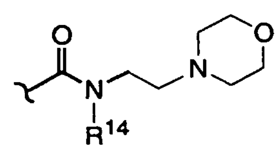
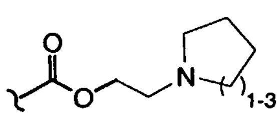
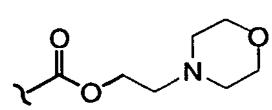
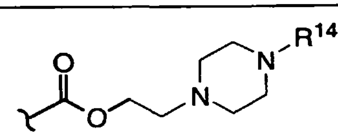
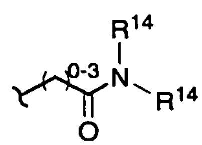
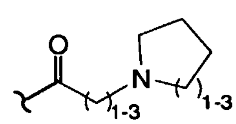
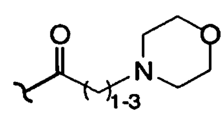
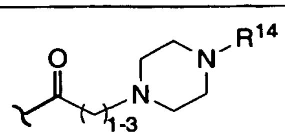
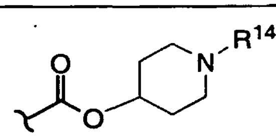
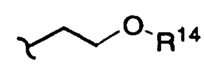
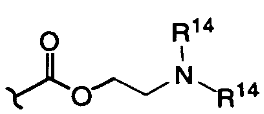
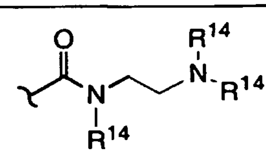
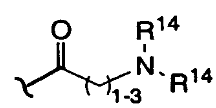
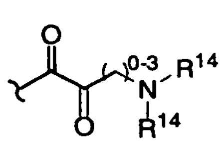
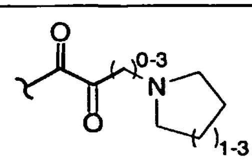
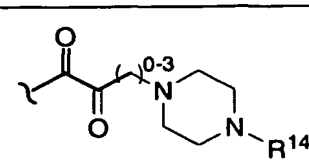
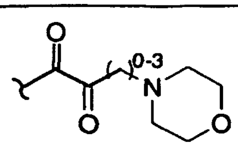
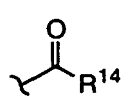
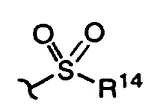
L^3 is $-O-$, $-NH-$, $-S(O)_{0-2}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)-$, $-NHC(O)-$, $-C_6H_4-$, or a direct bond;

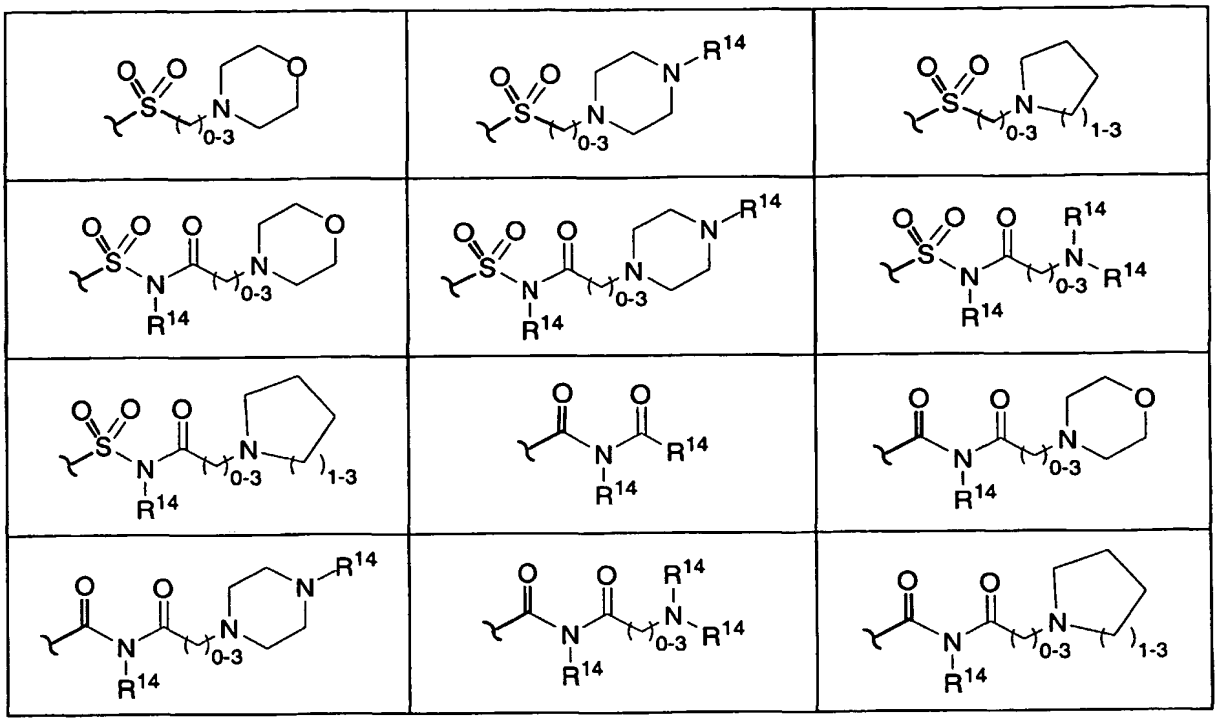
R^{51} is $-H$, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, $-CF_3$, $-OCF_3$, $-OH$, $-NH_2$, mono-C_1-C_6alkyl amino, di-C_1-C_6alkyl amino, $-SH$, $-CO_2H$, $-CN$, $-NO_2$, $-SO_3H$, or a saturated or mono- or poly- unsaturated C_5-C_{14}-mono- or fused poly- cyclic hydrocarbyl, optionally containing one or two annular heteroatoms per ring and optionally substituted with one, two, or three substituents;

wherein n is 0, 1, 2, or 3;

provided that an O or S is not singly bonded to another O or S in a chain of atoms.

16. The compound according to claim 15, wherein $-L^1-R^1$ is selected from:

$-R^{14}$		
		
		
		
		
		
		
		
		



wherein each R^{14} is independently selected from -H, $-(CH_2)_{1-3}CO_2H$, alkyl, alkoxy, alkenyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl.

17. The compound according to claim 16, wherein Z is $-C(R^{15})=$ or -C(H)=; L^4 is -O-; and p is at least one.

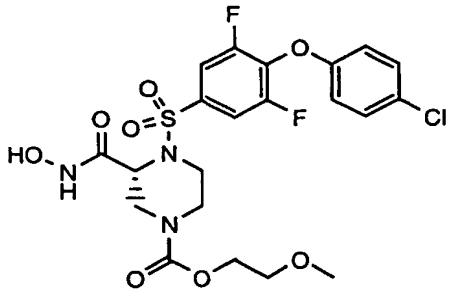
18. The compound according to claim 17, wherein Ar is selected from the group consisting of phenyl, biphenyl, napthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

19. The compound according to claim 18, wherein Ar is phenyl, optionally substituted, with at least one halogen.

20. The compound according to claim 19, wherein p is at least two.

21. The compound according to claim 20, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_2OR^{14}$.

22. The compound according to claim 21, having the structure:



23. The compound according to claim 16, wherein Z is -N=; and L^4 is -O-.

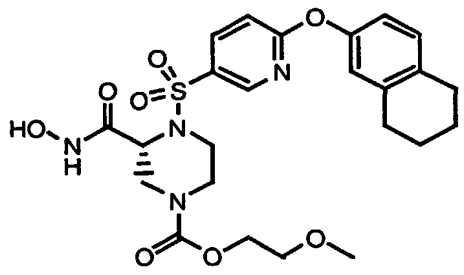
24. The compound according to claim 23, wherein Ar is selected from the group consisting of phenyl, biphenyl, napthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

25. The compound according to claim 24, wherein Ar is optionally substituted tetrahydro-naphthalene.

26. The compound according to claim 25, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.

27. The compound according to claim 26, wherein p is zero.

28. The compound according to claim 27, having the structure:



29. The compound according to claim 16, wherein Z is -N=; and L^4 is nothing.

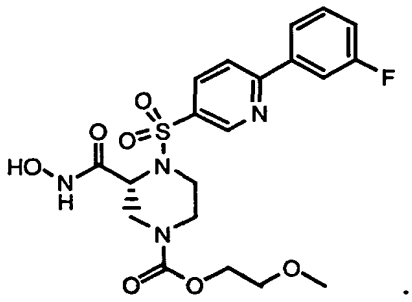
30. The compound according to claim 29, wherein Ar is selected from the group consisting of phenyl, biphenyl, napthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

31. The compound according to claim 30, wherein p is zero.

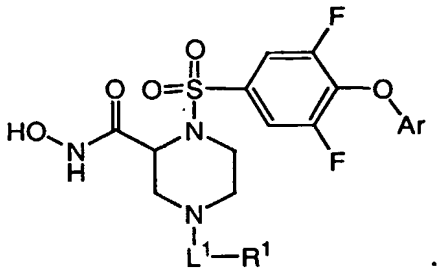
32. The compound according to claim 31, wherein Ar is optionally substituted phenyl.

33. The compound according to claim 32, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.

34. The compound according to claim 33, having the structure:



35. The compound according to claim 16, of formula **V**,

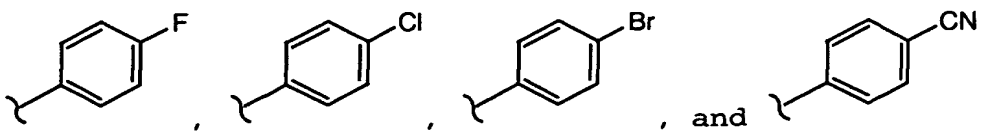


V

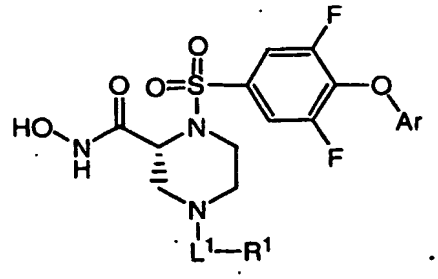
36. The compound according to claim 35, wherein Ar is selected from the group consisting of phenyl, biphenyl, napthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

37. The compound according to claim 36, wherein Ar is phenyl, optionally substituted, with at least one halogen.

38. The compound according to claim 36; wherein Ar is selected from,



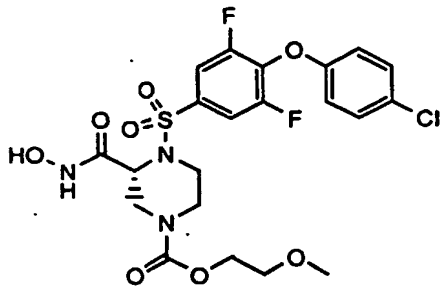
39. The compound according to claim 37, wherein the absolute stereochemistry is according to formula **VI**,



VI

40. The compound according to claim 39, wherein $-L^1-R^1$ is $-C(=O)OR^{14}$ or $-(CH_2)_{2-3}OR^{14}$.

41. The compound according to claim 40, having the structure:

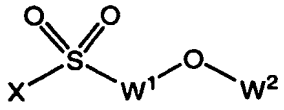


42. A pharmaceutical composition comprising a compound as described in any of claims 1 -41 and a pharmaceutically acceptable carrier.

43. A method of treating cancer, arthritis, and diseases related to angiogenesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 41.

44. A method of modulating the activity of Adam-10 comprising administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 41.

45. A method of making a bis-aryl ether sulfonyl halide according to formula **VII**:



VII

wherein X is a halide; and W^1 and W^2 are each independently an optionally substituted aryl, the method comprising: (a) combining a metal-aryloxide salt of a corresponding hydroxide-substituted aryl compound with a fluoro-substituted nitro aryl compound to make a bis-aryl ether nitro-aromatic compound; (b) reducing a nitro group of the bis-aryl ether nitro-aromatic compound to produce a corresponding aniline derivative; and (c) converting the corresponding aniline derivative to the bis-aryl ether sulfonyl halide.

46. The method of claim 45, wherein (a) – (c) are performed in the order described.

47. The method of claim 46, wherein the metal-aryloxide salt is combined with the fluoro-substituted nitro aryl in an organic solvent.

48. The method of claim 47, wherein the organic solvent comprises at least one of DMF and acetonitrile.

49. The method of claim 48, wherein the metal-aryloxide salt comprises at least one of a cesium salt and a potassium salt.

50. The method of claim 49, wherein the corresponding aniline derivative is converted to the bis-aryl ether sulfonyl halide via a diazonium intermediate of said corresponding aniline derivative.

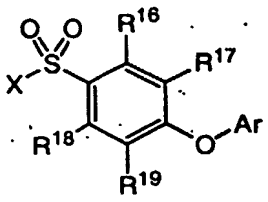
51. The method of claim 50, wherein the fluoro-substituted nitro aryl compound is 3,4,5-trifluornitrobenzene.

52. The method of claim 51, wherein the metal-aryloxide salt is a cesium salt.

53. The method of claim 52, wherein the corresponding hydroxide-substituted aryl compound is 4-chlorophenol.

54. The method of claim 53, wherein the bis-aryl ether sulfonyl halide is 4-(4-chlorophenoxy)-3,5-difluorophenylsulfonyl chloride.

55. A sulfonyl halide according to formula **VIII**:



VIII

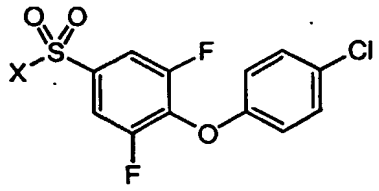
wherein X is halogen; R^{16}, R^{17}, R^{18}, and R^{19}, are each independently either -H or -F; and Ar is aryl or heteroaryl, each optionally substituted.

56. The sulfonyl halide of claim 55, wherein R^{16} and R^{18} are each -H; and R^{17} and R^{19} are each -F.

57. The sulfonyl halide of claim 56, wherein Ar is selected from the group consisting of phenyl, biphenyl, napthyl, tetrahydronaphthalene, chromen-2-one, dibenzofuran, pyryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl, each optionally substituted.

58. The sulfonyl halide of claim 57, wherein Ar is phenyl, optionally substituted, with at least one halogen.

59. The sulfonyl halide of claim 58, of formula **IX**:



IX

60. The sulfonyl halide of claim 59, wherein X is -Cl.